IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application	:	Confirmation No. 3863
Serial No. 10/581,322	:	Mail Stop: AF
Yoshikazu FUKUI et al.	:	Attorney Docket No. 2006_0755A
Filed July 18, 2006	:	Group Art Unit 1626
ISOXAZOLE DERIVATIVES AS PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS AGONISTS	:	Examiner Sun Loewe

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RULE 132 DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ken-ichi Matsumura, the undersigned, a citizen of Japan, residing at Umaminaka 16-15, Kouryou-cyou, Kitakaturagigun, Nara, Japan, do hereby declare:

1. That I am a co-inventor of the above-identified application.

2. That I graduated from Osaka University, Japan on March 31, 1993 with a degree in pharmaceutical science, and received the Ph.D. degree at Osaka University in 2004.

3. Since 1993, I have been a number of Shionogi & Co., Ltd., Osaka, Japan, and had engaged in the works of search for medicinal chemistry.

4. I am an author or co-authour of "J. Med. Chem. 2002, *45*, 2041", "Bioorg. Med. Chem. 2002, *10*, 3956", "J. Org. Chem. 2002,

67, 7741" etc. and a co-inventor of "WO1998/008836" etc.

5. That in order to show the novelty and unobviousness of the claimed invention of the above-identified application, I have under my control and direction conducted the following experiments. The remarks and experimental data are set forth herein below.

The Remarks and Experimental Data:

The Examiner cited Filzen et al. (WO03/084916) as prior art in the Office Action dated January 22, 2008. The difference between prior art and our Claims is "the substituent at the 4-position of the isoxazole" (R^2 in our Claims) as the Examiner pointed out. Therefore, we described the EC_{50} value for PPARδ of the reference compound wherein R^2 is hydrogen is much higher than that of the compound of the present invention in the remarks filed on May 22, 2008. However, the Examiner described that "A 4-fold difference is not considered to be a significant change as to indicate unexpected results."

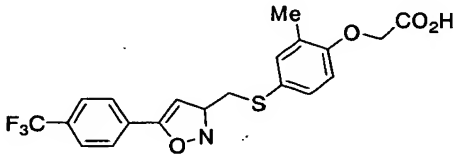
The compound ß-1-3 (Table 166) wherein R^2 is methyl shows EC_{50} value of 9.9 nM, which is 4-times more potent than that of "Reference compound" (R^2=H, EC_{50}=37 nM). It was well-known that high in-vitro potency as well as in vivo drug disposition can cause the reduction of dose of drug. Thus, ß-1-3 has potential to be a 4-times lower-dose drug compared to the reference compound. So, we think that the 4-times EC_{50} increase of ß-1-3 is very significant.

Additionally, the comparison data between a reference compound wherein R^2 is

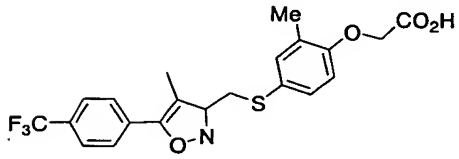
hydrogen and the compounds of the present invention are shown below.

We also synthesized β-1-15, Compound 1 and 2, which have CO_2Me, CH_2OMe and CH_2OEt groups at R^2 position (Figure 1). Surprisingly, their EC_{50} values, which are 1.4 nM, 1.5 nM and less than 1 nM respectively, are more than 25 times lower than that of reference compound. These results indicate that a substituent at R^2 poison is needed to demonstrate very strong PPARδ activity.

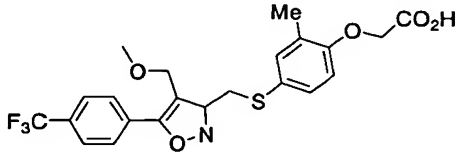
Figure 1.



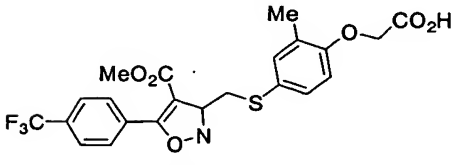
Reference compound EC50 = 37 nM



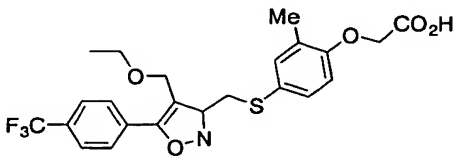
β-1-3 EC50 = 9.9 nM



β-1-15 EC50 = 1.5 nM



Compound 1 EC50 = 1.4 nM



Compound 2 EC50 < 1 nM

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and

the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: November 18, 2008

Ken-ichi Matsumura, Ph.D.